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Description

This invention relates inter alia to compositions for the stimulation of tear secretion with topically applied gastrointestinal hormones and/or biologically active peptides which activate the vasoactive intestinal peptide (VIP) receptors of lacrimal gland tissue. There are numerous situations where it is desirable to increase the amount and/or to modify the nature of tear fluid produced by the eye. Illustrative instances include the treatment of a spectrum of dry eye disorders including, but not limited to, keratoconjunctivitis sicca, age-related dry eye, Stevens-Johnson syndrome, ocular cicatricial pemphigoid, blepharitis, neurotrophic ocular surface disease, and corneal exposure. In addition, patients who wear contact lenses may have sub-optimal rates of tear production for optimal contact lens wear. Increased tear production is likely to increase eye comfort and contact lens comfort and improve contact lens wear. These patients will therefore benefit from agents that increase tear production.

Many different agents have been found to stimulate fluid secretion in the pancreas. Study of the pancreas has defined a spectrum of potential receptors by which agents may be capable of stimulating as well as modifying fluid secretion in other exocrine glands. These receptors have been reviewed by Gardner and Jensen, in the American Journal of Physiology 238:G63-G66, 1980. These receptors in the pancreas, named by any one of several agents that activate them, have been designated (1) Cholinergic (2) Cholecystokinin (CCK) (3) Bombesin (4) Physalaemin (5) Vasoactive Intestinal Peptide (VIP) and (6) Cholera Toxin. It is common to be able to add or delete a portion of the amino-acid chain or even produce small modifications of some of the amino acid sequences and still have hormones or peptides that interact with the same receptor class. Therefore, precursors, derivatives or fragments of these agents may also effectively activate the receptors to stimulate fluid secretion.

In the cat, it is known that VIP is contained in the parenchyma of the lacrimal gland and in the cholinergic sphenopalantine ganglion, but its role, if any, in these locations has been unknown (Johansson and Lundberg, Neuroscience 6:847, 1981; Uddman et al, Invest Opthlamol Vis Sci. 19:878, 1980). VIP has also been found in the parenchyma of the rat exorbital lacrimal gland and has been found to stimulate protein secretion in vitro (Dartt et al, Am J Physio 247:G502, 1984). Stolze and Sommer (International Tear Film Symposium, 1984, Lubbock, Texas) demonstrated that VIP administered intravenously to rabbits can stimulate main (orbital) lacrimal gland secretion.

What is needed are agents which will stimulate tear secretion by topical administration to the ocular surface. A topical mode of administration has several advantages. It eliminates the need for injections in patients with dry eye disorders, thereby decreasing systemic effects, cost of therapy, and the amount of drug needed.

Accordingly, it is an object of this invention to provide an improved agent for topical application to improve eye comfort. It is another object of the present invention to provide an improved agent for topical application to enhance contact lens wear and comfort.

The present invention provides the use of a compound which activates vasoactive intestinal peptide receptors of accessory lacrimal glands and is selected from the group consisting of vasoactive intestinal peptide, secretin and glucagon and their active precursors, derivatives, analogues and fragments, for the manufacture of a medicament for stimulating tear fluid secretion in humans and other animals when administered topically to the ocular surface. The invention is useful in the treatment of dry eye disorders and facilitates the treatment of dry eye disorders by eliminating the need for injections.

A preparation has also been discovered which when applied topically stimulates lacrimal gland secretion. The preparation contains at least one compound which activates vasoactive intestinal peptide receptors of the lacrimal gland tissue and is selected from the group consisting of vasoactive intestinal peptide, secretin and glucagon and their active precursors, derivatives, analogues and fragments. It may also contain a physiologically compatible vehicle and may also contain an ophthalmic preservative. These compounds may be used alone or in combination with one another.

Several modes of topical administration may be used in the practice of the invention. For example, the compounds can be administered topically to the eye as a drop, or within ointments, gels, or liposomes. Further, the compounds can be infused into the tear film by means of a pump-catheter system. In other embodiments the compounds are attached to and/or incorporated into contact lenses or contained within or carried by continuous or other selective-release devices including membranes.

The development of agents effective in stimulating lacrimal secretion when applied topically to the eye is unexpected for several reasons. First, the main lacrimal gland is not exposed to the surface of the eye; rather, it lies separated from the ocular surface by a relatively great diffusion distance. The main lacrimal gland is connected to the surface only through a series of microscopic ducts. Therefore, while drugs injected vascularly can reach the main lacrimal gland parenchyma, it is

unlikely that topically applied drugs will do so. Second, although there are microscopic nests of accessory lacrimal gland tissue within the conjunctiva, one expects that drugs will not penetrate the luminal tight junctions of the duct and acinar cells to the deep basolateral membranes. It is assumed, based on study of the pancreas, that receptors which initiate secretion are located in the deep basolateral membranes. Third, given that the accessory glands are understood to function somewhat independently from the main lacrimal gland, it is deemed unlikely that drugs that stimulate the main gland would stimulate the accessory glands even if penetration were adequate.

In the accompanying drawings:

Figures 1A, 1B, and 1C represent results obtained from practice of the invention with rabbits.

Figure 1A is a graph of the osmolality of tear samples, as a function of time, taken from a rabbit eye treated with 10 µl of buffer solution and, subsequently, the some eye treated in accordance with the invention with 10 µl of buffer solution containing 2×10^{-8} M VIP.

Figure 1B is a graph of the osmolality of tear samples, as a function of time, taken from a rabbit eye treated with 10 µl of buffer solution and, subsequently, the same eye treated in accordance with the invention with 10 µl of buffer solution containing 2×10^{-7} M VIP.

Figure 1C is a graph of the osmolality of tear samples, as a function of time, taken from a rabbit eye treated with 10 µl of buffer solution and, subsequently, the same eye treated in accordance with the invention with 10 µl of buffer solution containing 2×10^{-6} M VIP.

Figures 2A, 2B, and 2C represent results obtained from further practice of the invention with rabbits.

Figure 2A is a graph of the osmolality of tear samples, as a function of time, taken from a rabbit eye treated with 10 µl of buffer solution and, subsequently, the same eye treated in accordance with the invention with 10 µl of buffer solution containing 2×10^{-8} M VIP.

Figure 2B is a graph of the osmolality of tear samples, as a function of time, taken from a rabbit eye treated with 10 µl of buffer solution and, subsequently, the same eye treated in accordance with the invention with 10 µl of buffer solution containing 2×10^{-7} M VIP.

Figure 2C is a graph of the osmolality of tear samples, as a function of time, taken from a rabbit eye treated with 10 µl of buffer solution and, subsequently, the same eye treated in accordance with the invention with 10 µl of buffer solution containing 2×10^{-6} M VIP.

Figures 3A and 3B represent results obtained from further practice of the invention with rabbits.

Figure 3A is a graph of the osmolality of tear samples, as a function of time, taken from a rabbit eye treated with 10 µl of buffer solution and, subsequently, the same eye treated in accordance with the invention with 10 µl of buffer solution containing 2×10^{-6} M VIP.

Figure 3B is a graph of the osmolality of tear samples, as a function of time, taken from a rabbit eye treated with 10 µl of buffer solution, followed by treatment with 10 µl of buffer solution containing 2×10^{-4} M CCK, and, subsequently, the same eye treated in accordance with the invention with 10 µl of buffer solution containing 2×10^{-6} M VIP.

Figure 4 is a graph of the radioactivity present in the tear film, as a function of time, after instillation of 10 µl of a radioactive buffer solution, and after instillation of 10 µl of a radioactive buffer solution containing 2×10^{-6} M VIP, demonstrating the elimination of tracer substance from the tear film.

Figure 5 is a graph of radioactivity present in the tear film, as a function of time, after instillation of 10 µl of a radioactive, buffer solution and 10 µl of a radioactive buffer solution containing 2×10^{-6} M VIP demonstrating the elimination of tracer substance from the tear film.

Figures 6A, 6B and 6C represent results obtained from further practice of the invention with rabbits.

Figure 6A is a graph of the osmolality of tear samples as a function of time taken from a rabbit eye treated with 10 µl of buffer solution and the same eye treated in accordance with the invention with 10 µl of buffer solution containing 2×10^{-6} M glucagon.

Figure 6B is a graph of the osmolality of tear samples, as a function of time, taken from a rabbit eye treated with 10 µl of buffer solution and, subsequently, the same eye treated in accordance with the invention with 10 µl of buffer solution containing 2×10^{-5} M glucagon.

Figure 6C is a graph of the osmolality of tear samples, as a function of time, taken from a rabbit eye treated with 10 µl of buffer solution and, subsequently, the same eye treated in accordance with the invention with 10 µl of buffer solution containing 2×10^{-4} M glucagon.

Figures 7A, 7B and 7C represents results obtained from further practice of the invention with rabbits.

Figure 7A is a graph of the osmolality of tear samples, as a function of time, taken from a rabbit eye treated with 10 µl of buffer solution and, subsequently, the same eye treated in accordance with the invention with 10 µl of buffer solution containing 2×10^{-7} M secretin.

Figure 7B is a graph of the osmolality of tear samples, as a function of time, taken from a rabbit eye treated with 10 µl of buffer solution and, subsequently, the same eye treated in accordance with the invention with 10 µl of buffer solution containing 2×10^{-6} M secretin.

Figure 7C is a graph of the osmolality of tear samples as a function of time taken from the eye treated with 10 µl of buffer solution and the same eye treated with 10 µl of buffer solution containing 2×10^{-5} M secretin.

In accordance with the invention, tear secretion is stimulated with topically applied compounds of the type defined in claim 1.

A preparation according to the invention can, by way of non-limiting illustration, be applied to the eye in animals and humans as a drop or within ointments, gels, or liposomes. Further, the compounds can be infused into the tear film via a pump-catheter system. In other embodiments, the compounds can be contained within or carried by continuous or other selective-release devices, for example, membranes, such as but not limited to those used in the Ocusert^{R} system (Alza Corp., Palo Alto, CA). They also can be attached to, carried by and/or contained within contact lenses that are placed on the eye. In general, it is desired that the mode of application be such that the compound enters the tear film or otherwise makes contact with the surface of the eye.

In vivo examples of the invention were conducted on rabbits with dry eyes. The dry eye disorder is created by surgically closing the duct that carries fluid from the main lacrimal gland to the tear film and surgically removing the nictitans and harderian glands. This leaves intact only the accessory glands that lie on the ocular surface. These rabbits develop increased tear film osmolality soon after the operation, a finding that is understood to be due to decreased tear production, and that is characteristic of dry eye. It is recognized that results of ophthalmologic tests using rabbits has close correlation with humans, and therefore the results carry over to humans.

The effect of topically applied isotonic buffer solution with and without VIP on tear film osmolality was studied in the dry eye rabbit. All test drops were ten µl in volume and were applied in each case six minutes after the instillation of proparacaine, which anesthetizes the surface of the eye and prevents reflex tearing. Tear samples were taken with a micropipette system, in the manner described in the article entitled "Osmolarity of Tear Microvolumes in Keratoconjunctivitis Sicca", by Gilbard et al, Arch Ophthalmol 96:677, 1978. Osmolality was measured by freezing-point depression.

The following protocol was used for each drop tested. Six minutes prior to instillation of the test drop proparacaine was instilled. At zero time a tear sample was taken for measurement of osmolality. At one minute the test drop was instilled. At six and at sixteen minutes, tear samples were taken for osmolality measurements. The procedure for instilling each test drop is that the drop of buffered solution was first instilled in the dry eye and measurements were taken followed by a drop of buffered solution containing VIP. The following test drops were instilled: 1) buffer solution, 2) buffer solution containing 2×10^{-8} M VIP, 3) buffer solution, 4) buffer solution containing 2×10^{-7} M VIP, 5) buffer solution, 6) buffer solution containing 2×10^{-6} M VIP. The results are shown in Figures 1A, 1B, and 1C and Figures 2A, 2B, and 2C, where Figures 1 and 2 each represent the results obtained from the same rabbit.

As shown in Figures 1 and 2, buffer solution containing VIP lowers the tear film osmolality more effectively than buffer solution alone. The Figures also indicate that VIP produced a dose-dependent decrease in tear film osmolality, and the decrease was strikingly more pronounced than the effect of buffer alone. This reflects a VIP stimulated dose-dependent increase in tear secretion.

In a similar protocol the effect of topically applied CCK on tear secretion was tested. CCK, like VIP, had been found to stimulate lacrimal gland secretion when administered intra-arterially. CCK did not lower tear osmolality more effectively than a placebo, as shown in Figure 3B. In the same experiment, VIP decreased tear film osmolality more effectively than a placebo in one of two trials. It accordingly appears, without apparent reason, that CCK, unlike VIP, does not stimulate tear secretion when applied topically to the eye.

In a separate example, dry eye rabbits were studied by examining the rate of elimination of a tracer substance technetium, Tc^{99m}, as sodium pertechnetate from the tear film. Essentially equivalent counts of Tc^{99m} were placed in 10 µl of, in some instances, a buffer solution to serve as a control, and in other instances, a buffer solution containing 2×10^{-6} M VIP. Radioactivity present in the tear film was measured over contiguous fifteen second periods for thirty minutes with a gamma camera, and the measurements stored on a computer. The following protocol was used: Rabbits were anaesthetized with IM rompun (Registered Trade Mark) and ketamine. At zero time proparacaine was applied. At five minutes, the radioactive buffer with VIP was instilled in the eye. Radioactivity present in the tear film was then recorded as described. After thirty minutes, proparacaine was again instilled in the eye and the procedure repeated with radioactive buffer alone. As shown in Figure 4, the slope of the elimination curve for VIP over the first fifteen minutes after drop instillation is markedly

steeper than the curve for buffer without VIP (slope for first 15 minutes is -1.65 vs -0.82 slope thereafter). This increased rate of tracer washout is understood to be indicative of increased tear secretion. In a second similar experiment, the effect of VIP was first tested, and then radioactive buffer alone, and then the effect of VIP again. As shown in Figure 5, the slope of the elimination curves for both VIP tests were substantially steeper than for radioactive buffer alone, confirming again that topically applied VIP stimulates tear secretion.

In separate experiments, the effect of topically applied isotonic buffer solution with or without glucagon or secretin on tear film osmolarity was studied in dry eye rabbits. All test drops were ten µl in volume. Tear osmolality was measured one minute prior to drop instillation and five and fifteen minutes after drop instillation. A drop of buffered solution was first instilled in the dry eye and measurements were taken followed by a drop of buffered solution containing glucagon or secretin, depending on the test.

The effect of topically applied glucagon was studied with the instillation of drops in the following order: 1) buffer solution, 2) buffer solution containing 2×10^{-6} M glucagon, 3) buffer solution, 4) buffer solution containing 2×10^{-5} M glucagon, 5) buffer solution, 6) buffer solution containing 2×10^{-4} M glucagon. The results are shown in Figures 6A, 6B, and 6C, all of which represent results from the same rabbit. As shown in Figure 6, buffer solution containing glucagon lowers tear film osmolality more effectively than buffer solution alone. The figure also indicates that glucagon produces a dose-dependent decrease in tear film osmolality and the decrease is more pronounced than the effect of buffer alone. This reflects a glucagon stimulated dose-dependent increase in tear secretion.

The effect of topically applied secretin was studied with the instillation of drops in the following order: 1) buffer solution, 2) buffer solution containing 2×10^{-7} M secretin, 3) buffer solution, 4) buffer solution containing 2×10^{-6} M secretin, 5) buffer solution, 6) buffer solution containing 2×10^{-5} M secretin. The results are shown in Figures 7A, 7B and 7C, all of which represents results from the same rabbit. As shown in Figure 7, buffer solution containing secretin lowers tear film osmolality more effectively than buffer solution alone. The Figure also indicates that secretin produces a dose-dependent decrease in tear film osmolality and the decrease is more pronounced than the effect of buffer alone. This reflects a secretin stimulated dose-dependent increase in tear secretion.

Further in accordance with the invention, a tear-stimulation preparation is made by combining a compound as defined in claim 1 with an appropriate preservative. The preparation may also contain a physiologically compatible ophthalmic vehicle as those skilled in the art can select using conventional criteria. The vehicles may be selected from the known ophthalmic vehicles which include but are not limited to polyethers such as polyethylene glycol, polyvinyls such as polyvinyl alcohol and povidone, cellulose derivatives such as methylcellulose and hydroxypropyl methylcellulose, petroleum derivatives such as mineral oil and white petrolatum, animal fats such as lanolin, vegetable fats such as peanut oil, polymers of acrylic acid such as carboxypolymethylene gel, polysaccharides such as dextrans, and glycosaminoglycans such as sodium hyaluronate and salts such as sodium chloride and potassium chloride. One preferred vehicle is the non-toxic ophthalmic preparation with has the following composition: 22.0 to 43.0 mmol/l of potassium; 29.0 to 50.0 mmol/l of bicarbonate; 130.0 to 140.0 mmol/l of sodium; and 118.0 to 136.5 mmol/l of chloride.

Preferred preservatives are physiologically compatible and do not inactivate the hormone or peptide. Preservatives include but are not limited to alcohols such as chlorobutanol, though other appropriate preservatives known to those skilled in the art may be used. As known, glucagan requires the additives glycerin and lactose to render it soluble.

Claims

Claims for the following Contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Use of a compound which activates vasoactive intestinal peptide receptors of accessory lacrimal glands and is selected from the group consisting of vasoactive intestinal peptide, secretin and glucagon and their active precursors, derivatives, analogues and fragments, for the manufacture of a medicament for stimulating tear fluid secretion in humans and other animals when administered topically to the ocular surface.

2. The use according to claim 1, wherein said medicament (a) is adapted for infusion of the compound into the tear film by means of a pump-catheter system; or (b) is a selective-release device for contacting said ocular surface with the compound; or (c) comprises said compound in association with contact lenses; or (d) comprises drops, or a gel, ointment or liposome containing said compound.

3. A Pharmaceutical preparation comprising an ophthalmic preservative and at least one compound which activates vasoactive intestinal

peptide receptors of accessory lacrimal glands and is selected from the group consisting of vasoactive intestinal peptide, secretin and glucagon and their active precursors, derivatives, analogues and fragments.

4. A preparation according to claim 3 further comprising a physiologically compatible ophthalmic vehicle, for example any of polyethers, polyvinyls, cellulose derivatives, petroleum derivatives, polymers of acrylic acid, animal fats, vegetable fats, glycosamino glycans, and polysaccharides.

5. A preparation according to claim 3, wherein said compound is vasoactive intestinal peptide, and said preservative comprises chlorobutanol, and the preparation further comprises a physiologically compatible ophthalmic vehicle comprising from 22.0 to 43.0 mmol/l of potassium; from 29.0 to 50.0 mmol/l of bicarbonate; from 130.0 to 140.0 mmol/l of sodium; and from 118.0 to 136.5 mmol/l of chloride.

6. A preparation adapted for only topical ophthalmic administration to the exclusion of oral and injectable administration, which composition comprises at least one compound which activates vasoactive intestinal peptide receptors of accessory lacrimal glands and is selected from the group consisting of vasoactive intestinal peptide, secretin and glucagon and their active precursors, derivatives, analogues and fragments; and an ophthalmically acceptable carrier therefor.

7. A preparation according to claim 6 in the form of a gel, ointment, liposome, drops, solution for infusion by means of a pump-catheter, a selective-release device, or a contact lens carrying said compound.

8. A preparation according to claim 3 wherein the preservative is an alcohol.

9. A preparation according to claim 8 wherein the alcohol is chlorobutanol.

10. A preparation according to claim 4 wherein the vehicle is the cellulose derivative methyl cellulose or hydroxypropyl cellulose.

Claims for the following Contracting State: AT

1. A method of preparing a pharmaceutical preparation comprising an ophthalmic preservative and at least one compound which activates vasoactive intestinal peptide receptors of accessory lacrimal glands and is selected from the group consisting of vasoactive intestinal peptide, secretin and glucagon and their active precursors, derivatives, analogues and fragments; which method comprises bringing the compound into association with the ophthalmic preservative, and an ophthalmologically acceptable carrier.

2. A method according to claim 1 wherein the preparation further comprises a physiologically compatible ophthalmic vehicle, for example any of polyethers, polyvinyls, cellulose derivatives, petroleum derivatives, polymers of acrylic acid, animal fats, vegetable fats, glycosamino glycans, and polysaccharides.

3. A method according to claim 1, wherein said compound is vasoactive intestinal peptide, and said preservative comprises chlorobutanol, and the preparation further comprises a physiologically compatible ophthalmic vehicle comprising from 22.0 to 43.0 mmol/l of potassium; from 29.0 to 50.0 mmol/l of bicarbonate; from 130.0 to 140.0 mmol/l of sodium; and from 118.0 to 136.5 mmol/l of chloride.

4. A method of preparing a preparation adapted for only topical ophthalmic administration to the exclusion of oral and injectable administration, which composition comprises at least one compound which activates vasoactive intestinal peptide receptors of accessory lacrimal glands and is selected from the group consisting of vasoactive intestinal peptide, secretin and glucagon and their active precursors, derivatives, analogues and fragments; and an ophthalmically acceptable carrier therefor, which method comprises bringing the compound into association with the ophthalmically acceptable carrier.

5. A method according to claim 4 wherein the preparation is in the form of a gel, ointment, liposome, drops, solution for infusion by means of a pump-catheter, a selective-release device, or a contact lens carrying said compound.

6. A method according to claim 1 wherein the preservative is an alcohol.

7. A method according to claim 6 wherein the alcohol is chlorobutanol.

8. A method according to claim 2 wherein the vehicle is the cellulose derivative methylcellulose or hydroxypropyl cellulose.

Revendications

Revendications pour les Etats contractants suivants: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Utilisation d'un composé qui active les récepteurs de polypeptide intestinal à action vaso-motrice des glandes lacrymales auxiliaires et qui est choisi dans le groupe comprenant le polypeptide intestinal à action vaso-motrice, la sécrétine, le glucagon et leurs précurseurs, dérivés, analogues et fragments actifs, pour la préparation d'un médicament propre à stimuler la sécrétion de liquide lacrymal chez les humains et d'autres animaux lorsqu'il est administré topiquement à la surface oculaire.

2. Utilisation selon la revendication 1, dans laquelle ledit médicament (a) est adapté pour l'injection du composé dans le film lacrymal au moyen d'un système à pompe-cathéter; ou (b) est un dispositif à libération sélective propre à mettre ladite surface oculaire en contact avec le composé; ou (c) comprend ledit composé en association avec des lentilles de contact; ou (d) est constitué par des gouttes ou par un gel, une pommade ou un liposome contenant ledit composé.

3. Préparation pharmaceutique, comprenant un stabilisant oculaire et au moins un composé qui active les récepteurs de polypeptide intestinal à action vaso-motrice des glances lacrymales auxiliaires et qui est choisi dans le groupe comprenant le polypeptide intestinal à action vaso-motrice, la sécrétine, le glucagon et leurs précurseurs, dérivés, analogues et fragments actifs.

4. Préparation selon la revendication 3, comprenant en outre un véhicule ophtalmique physiologiquement compatible, choisi par exemple parmi les polyéthers, les polyvinyles, les dérivés cellulosiques, les dérivés du pétrole, les polymères de l'acide acrylique, les graisses animales, les graisses végétales, les glycosaminoglucanes et les polysaccharides.

5. Préparation selon la revendication 3, dans laquelle ledit composé est le polypeptide intestinal à action vaso-motrice et ledit stabilisant comprend le chlorobutanol, la préparation contenant en outre un véhicule ophtalmique physiologiquement compatible comprenant de 22,0 à 43,0 mmole/l de potassium, de 29,0 à 50,0 mmole/l de bicarbonate, de 130,0 à 140,0 mmole/l de sodium et de 118,0 à 136,5 mmole/l de chlorure.

6. Préparation uniquement propre à l'administration ophtalmique topique à l'exclusion de l'administration orale ou parentérale, laquelle composition comprend au moins un composé qui active les récepteurs de polypeptide intestinal à action vaso-motrice des glandes lacrymales auxiliaires et qui est choisi dans le groupe comprenant le polypeptide intestinal à action vaso-motrice, la sécrétine, le glucagon et leurs précurseurs, dérivés, analogues et fragments actifs; et un excipient acceptable sur le plan ophtalmique pour ce composé.

7. Préparation selon la revendication 6 sous la forme d'un gel, d'une pommade, d'un liposome, de gouttes, d'une solution pour injection au moyen d'une pompe-catheter, d'un dispositif à libération sélective ou d'une lentille de contact portant ledit composé.

8. Préparation selon la revendication 3, dans laquelle le stabilisant est un alcool.

9. Preparation selon la revendication 8, dans laquelle l'alcool est le chlorobutanol.

10. Préparation selon la revendication 4, dans laquelle le véhicule est le dérivé cellulosique méthylcellulose ou hydroxypropylcellulose.

Revendications pour l'Etat contractant suivant: AT

1. Procédé de confection d'une préparation pharmaceutique comprenant un stabilisant ophtalmique et au moins un composé qui active les récepteurs de polypeptide intestinal à action vaso-motrice des glandes lacrymales auxiliaires et qui est choisi dans le groupe comprenant le polypeptide intestinal à action vasomotrice, la sécrétine, le glucagon et leurs précurseurs, dérivés, analogues et fragments actifs, lequel procédé consiste à mettre le composé en association avec le stabilisant ophtalmique et avec un excipient acceptable sur le plan ophtalmologique.

2. Procédé selon la revendication 1, dans lequel la préparation comprend en outre un véhicule ophtalmique physiologiquement compatible, choisi par exemple parmi les polyéthers, les polyvinyles, les dérivés cellulosiques, les dérivés du pétrole, les polymères de l'acide acrylique, les graisses animales, les graisses végétales, les glycosaminoglucanes et les polysaccharides.

3. Procédé selon la revendication 1, dans lequel

ledit composé est le polypeptide intestinal à action vaso-motrice et ledit stabilisant comprend du chlorobutanol, la préparation contenant en outre un véhicule ophtalmique physiologiquement compatible comprenant de 22,0 à 43,0 mmole/l de potassium, de 29.0 à 50,0 mmole/l de bicarbonate, de 130,0 à 140,0 mmole/l de sodium et de 118,0 à 136,5 mmole/l de chlorure.

4. Procédé de confection d'une préparation uniquement propre à l'administration ophtalmique topique à l'exclusion de l'administration orale ou parentérale, laquelle composition comprend au moins un composé qui active les récepteurs de polypeptide intestinal à action vaso-motrice des glandes lacrymales auxiliaires et qui est choisi dans le groupe comprenant le polypeptide intestinal à action vaso-motrice, la sécrétine, le glucagon et leurs précurseurs, dérivés, analogues et fragments actifs; et un excipient acceptable sur le plan ophtalmique pour ce composé; lequel procédé consiste à mettre le composé en association avec l'excipient acceptable sur le plan ophtalmique.

5. Procédé selon la revendication 4, dans lequel la préparation est sous la forme d'un gel, d'une pommade, d'un liposome, de gouttes, d'une solution pour injection au moyen d'une pompe-cathéter, d'un dispositif à libération sélective ou d'une lentille de contact portant ledit composé.

6. Procédé selon la revendication 1, dans lequel le stabilisant est un alcool.

7. Procédé selon la revendication 6, dans lequel l'alcool est le chlorobutanol.

8. Procédé selon la revendication 2, dans lequel le véhicule est le dérivé cellulosique méthylcellulose ou hydroxypropylcellulose.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verwendung einer Verbindung, die vasoaktive intestinale Peptidrezeptoren akzessorischer Tränendrüsen aktiviert und aus der aus vasoaktivem intestinalem Peptid, Sekretin und Glucagon und deren aktiven Vorstufen, Derivaten, Analogons und Fragmenten bestehenden Gruppe ausgewählt ist, zur Herstellung eines Medikaments zur Stimulierung der Tränenflüssigkeitssekretion in menschlichen und tierischen Lebewesen bei topischer Verabreichung auf die Augenoberfläche.

2. Verwendung nach Anspruch 1, bei der das Medikament a) geeignet ist für eine Infusion der Verbindung in den Tränenfilm mittels eines Pump-Katheter-Systems oder b) eine Selektivfreisetzungseinrichtung zum Kontaktieren der Augenoberfläche mit der Verbindung ist oder c) die Verbindung in Assoziation mit Kontaktlinsen umfaßt oder d) Tropfen oder ein Gel, eine Salbe oder ein Liposom, die Verbindung enthaltend, umfaßt.

3. Pharmazeutische Zubereitung, bestehend aus einem ophthalmischen Konservierungsmittel und zumindest einer Verbindung, die vasoaktive intestinale Peptidrezeptoren akzessorischer Tränendrüsen aktiviert und aus der aus vasoaktivem intestinalem Peptid, Sekretin und Glucagon und deren aktiven Vorstufen, Derivaten, Analogons und Fragmenten bestehenden Gruppe ausgewählt ist.

4. Zubereitung nach Anspruch 3, ferner bestehend aus einem physiologisch kompatiblen ophthalmischen Bindemittel, zum Beispiel eines aus Polyethern, Polyvinylen, Cellulosederivaten, Erdölderivaten, Polymeren der Acrylsäure, tierischen Fetten, pflanzlichen Fetten, Glycosaminoglycanen und Polysacchariden.

5. Zubereitung nach Anspruch 3, bei der die Verbindung vasoaktives intestinales Peptid ist und das Konservierungsmittel Chlorobutanol umfaßt, wobei die Zubereitung feiner ein physiologisch kompatibles ophthalmisches Bindemittel umfaßt, das von 22,0 bis 43,0 mmol/l Kalium, von 29,0 bis 50,0 mmol/l Bicarbonat, von 130,0 bis 140,0 mmol/l Natrium und von 118,0 bis 136,5 mmol/l Chlorid enthält.

6. Zubereitung, geeignet für nur topische ophthalmische Verabreichung unter Ausschluß von oraler und injizierbarer Verabreichung, welche Zusammensetzung zumindest eine Verbindung, die vasoaktive intestinale Peptidrezeptoren akzessorischer Tränendrüsen aktiviert und aus der aus vasoaktivem intestinalem Peptid, Sekretin und Glucagon und deren aktiven Vorstufen, Derivaten, Analogons und Fragmenten bestehenden Gruppen ausgewählt ist, und hierfür einen ophthalmisch akzeptablen Träger umfaßt.

7. Zubereitung nach Anspruch 6 in Form eines Gels, einer Salbe, eines Liposoms, von Tropfen, einer Lösung für eine Infusion mittels eines Pumpkatheters, einer Selektivfreisetzungs-

einrichtung oder einer Kontaktlinse, die Verbindung tragend.

8. Zubereitung nach Anspruch 3, bei der das Konservierungsmittel ein Alkohol ist.

9. Zubereitung nach Anspruch 8, bei der der Alkohol Chlorobutanol ist.

10. Zubereitung nach Anspruch 4, bei der das Bindemittel das Cellulosederivat Methylcellulose oder Hydroxypropylcellulose ist.

Patentansprüche für folgenden Vertragsstaat: AT

1. Verfahren zur Herstellung einer pharmazeutischen Zubereitung, bestehend aus einem ophthalmischen Konservierungsmittel und zumindest einer Verbindung, die vasoaktive intestinale Peptidrezeptoren akzessorischer Tränendrüsen aktiviert und aus der aus vasoaktivem intestinalem Peptid, Sekretin und Glucagon und deren aktiven Vorstufen, Derivaten, Analogons und Fragmenten bestehenden Gruppe ausgewählt ist, welches Verfahren darin besteht, daß die Verbindung mit dem ophthalmischen Konservierungsmittel und einem ophthalmologisch akzeptablen Träger in Assoziation gebracht wird.

2. Verfahren nach Anspruch 1, bei dem die Zubereitung ferner ein physiologisch kompatibles ophthalmisches Bindemittel, zum Beispiel eines aus Polyethern, Polyvinylen, Cellulosederivaten, Erdölderivaten, Polymeren der Acrylsäure, tierischen Fetten, pflanzlichen Fetten, Glycosaminoglycanen und Polysacchariden umfaßt.

3. Verfahren nach Anspruch 1, bei dem die Verbindung vasoaktives intestinales Peptid ist und das Konservierungsmittel Chlorobutanol umfaßt, wobei die Zubereitung ferner ein physiologisch kompatibles ophthalmisches Bindemittel umfaßt, das von 22,0 bis 43,0 mmol/l Kalium, von 29,0 bis 50,0 mmol/l Bicarbonat, von 130,0 bis 140,0 mmol/l Natrium und von 118,0 bis 136,5 mmol/l Chlorid enthält.

4. Verfahren zum Herstellen einer Zubereitung, geeignet für nur topische ophthalmische Verabreichung unter Ausschluß von oraler und injizierbarer Verabreichung, welche Zusammensetzung zumindest eine Verbindung, die vasoaktive intestinale Peptidrezeptoren akzessorischer Tränendrüsen aktiviert und aus der aus vasoaktivem intestinalem Peptid, Sekretin und Glucagon und deren aktiven Vorstufen, Derivaten, Analogons und Fragmenten bestehenden Gruppen ausgewählt ist, und hierfür einen ophthalmisch akzeptablen Träger umfaßt, welches Verfahren darin besteht,daß die Verbindung mit dem ophthalmischen akzeptablen Träger in Assoziation gebracht wird.

5. Verfahren nach Anspruch 4, mit der Zubereitung in Form eines Gels, einer Salbe, eines Liposoms, von Tropfen, einer Lösung für eine Infusion mittels eines Pumpkatheters, einer Selektivfreisetzungseinrichtungoder einer Kontaktlinse, die Verbindung tragend.

6. Verfahren nach Anspruch 1, bei dem das Konservierungsmittel ein Alkohol ist.

7. Verfahren nach Anspruch 6, bei dem der Alkohol Chlorobutanol ist.

8. Verfahren nach Anspruch 2, bei dem das Bindemittel das Cellulosederivat Methylcellulose oder Hydroxypropylcellulose ist.

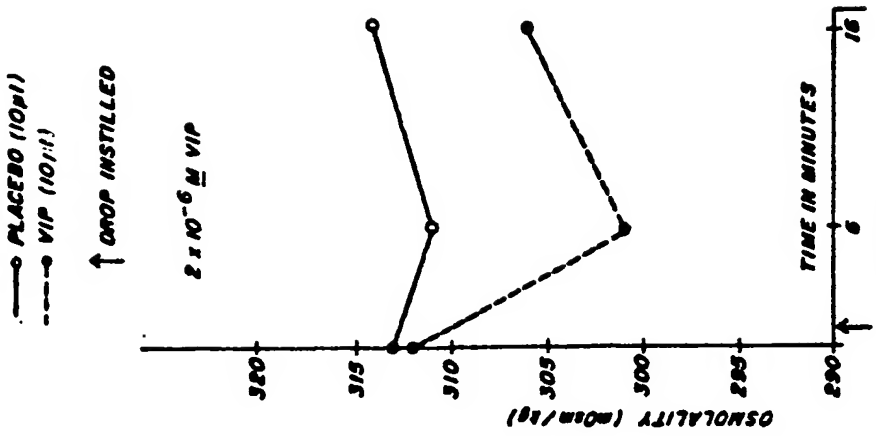

FIG. 1C

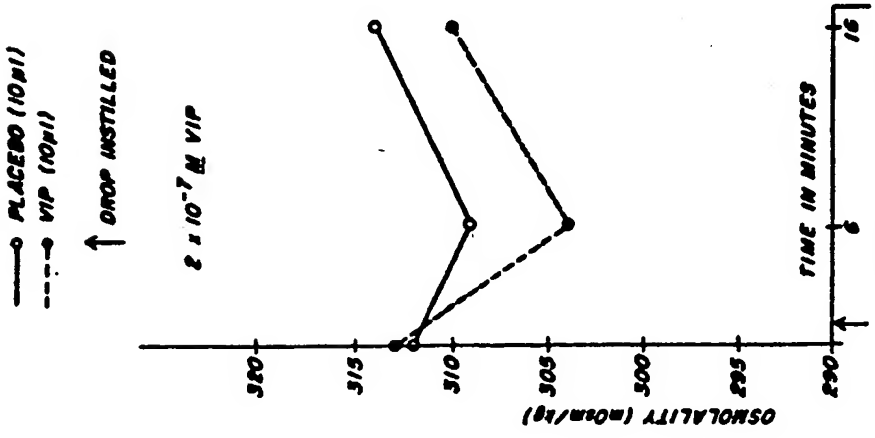

FIG. 1B

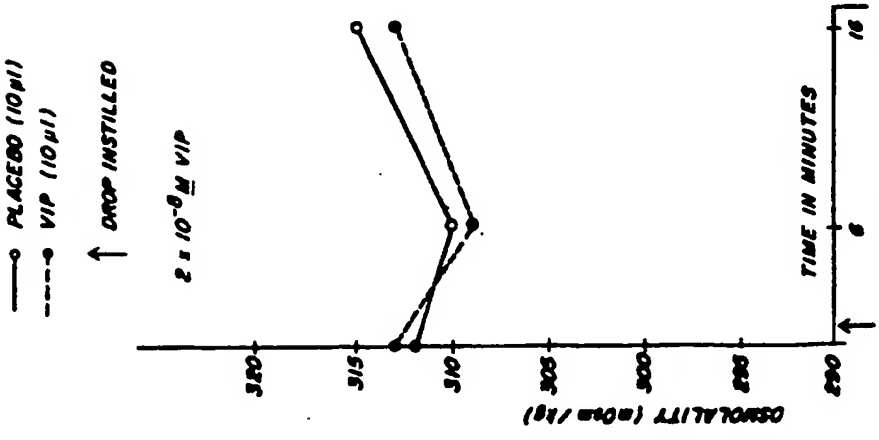

FIG. 1A

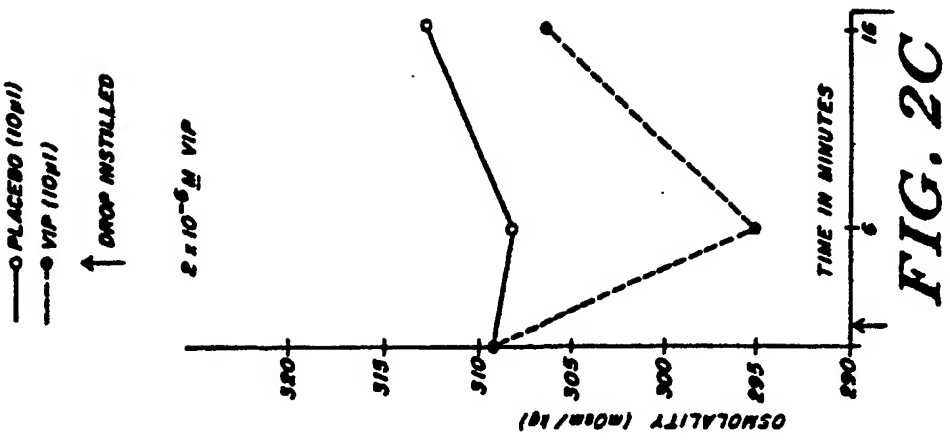

FIG. 2C

FIG. 2B

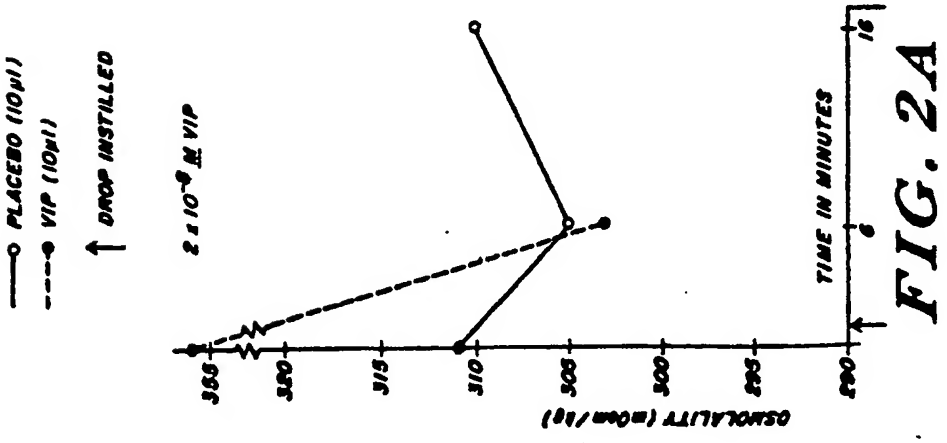

FIG. 2A

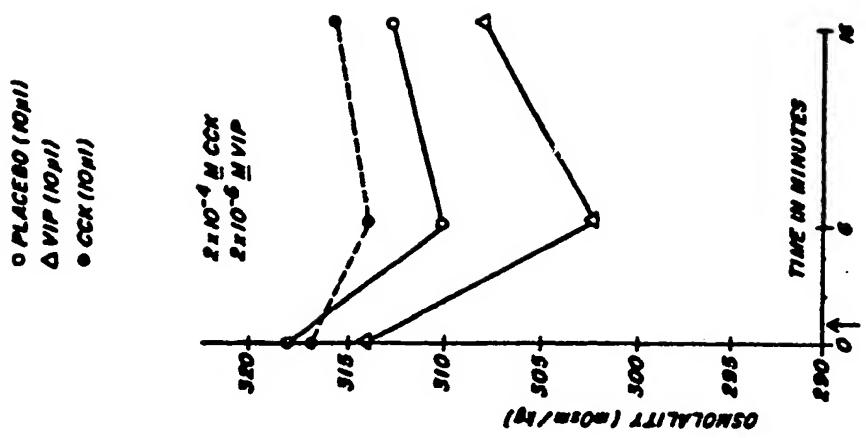
○ PLACEBO (10µl)
△ VIP (10µl)
● CCK (10µl)
2 x 10⁻⁴ M CCK
2 x 10⁻⁶ M VIP
OSMOLALITY (mOsm/kg)
320
315
310
305
300
295
290
TIME IN MINUTES
0
30
60

FIG. 3B

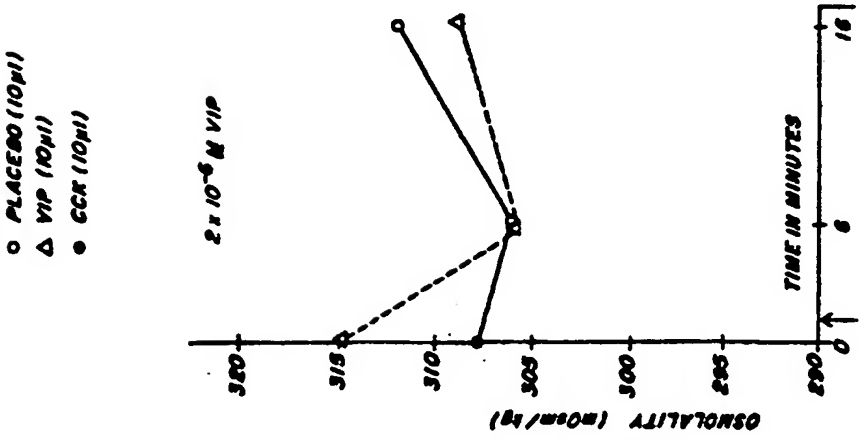
○ PLACEBO (10µl)
△ VIP (10µl)
● CCK (10µl)
2 x 10⁻⁶ M VIP
OSMOLALITY (mOsm/kg)
320
315
310
305
300
295
290
TIME IN MINUTES
0
30
60

FIG. 3A

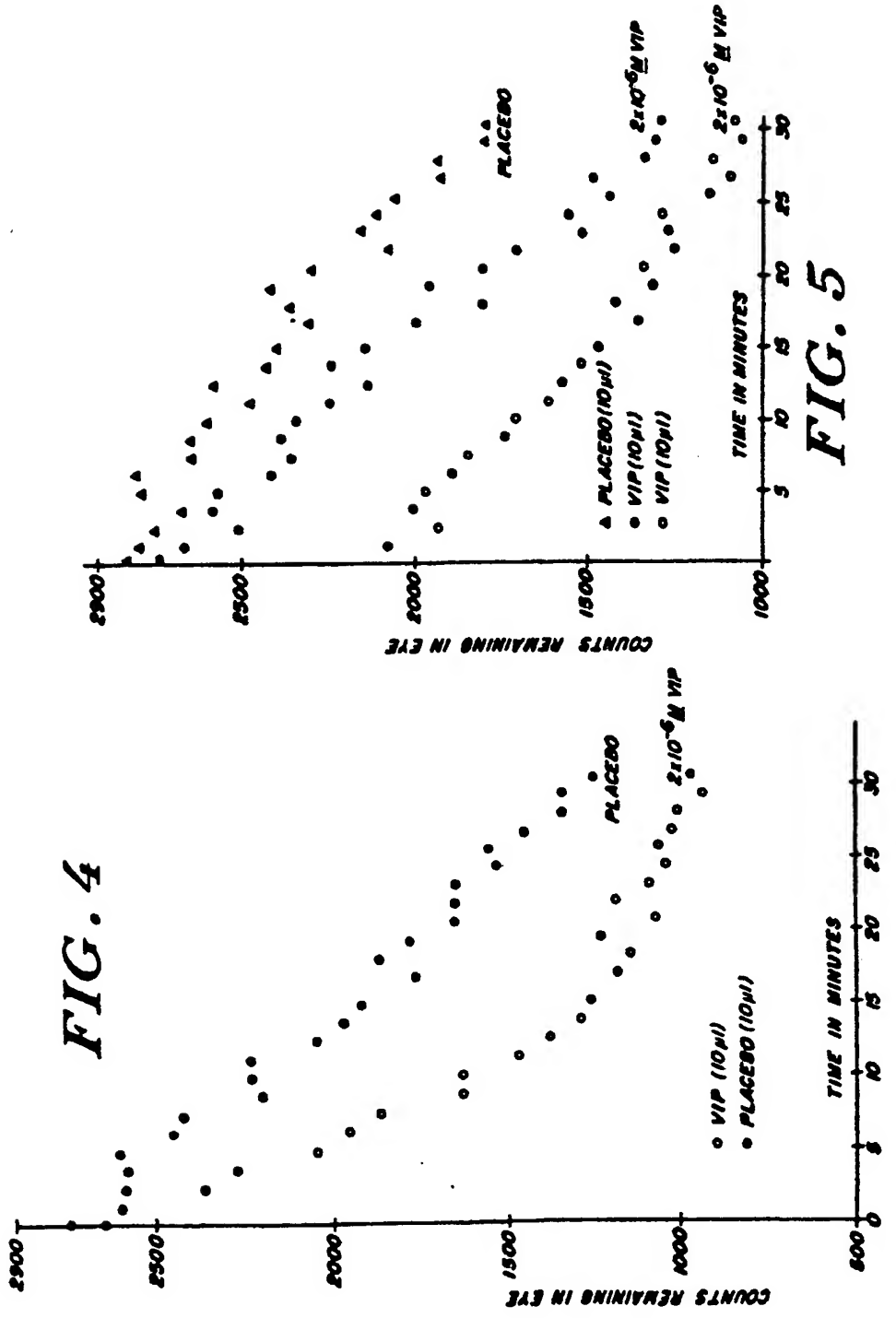
COUNTS REMAINING IN EYE
2500
2000
1500
1000
500
0
5
10
15
20
25
30
TIME IN MINUTES
VIP (10μl)
PLACEBO (10μl)
PLACEBO
2x10⁻⁶M VIP

FIG. 4

COUNTS REMAINING IN EYE
2500
2000
1500
1000
5
10
15
20
25
30
TIME IN MINUTES
PLACEBO(10μl)
VIP(10μl)
VIP(10μl)
PLACEBO
2x10⁻⁶M VIP
2x10⁻⁶M VIP

FIG. 5

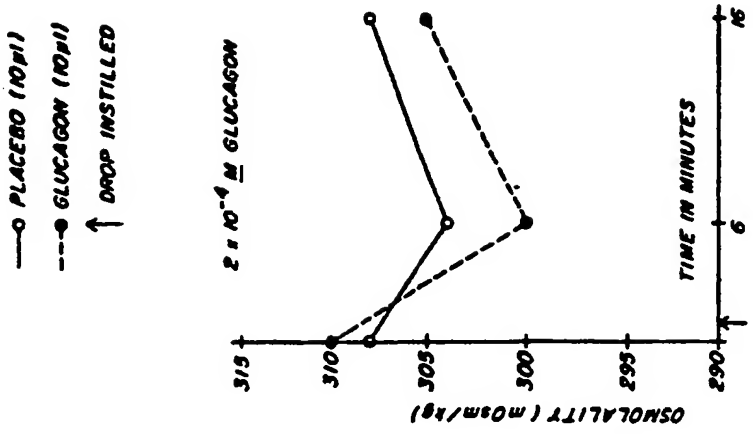

FIG. 6C

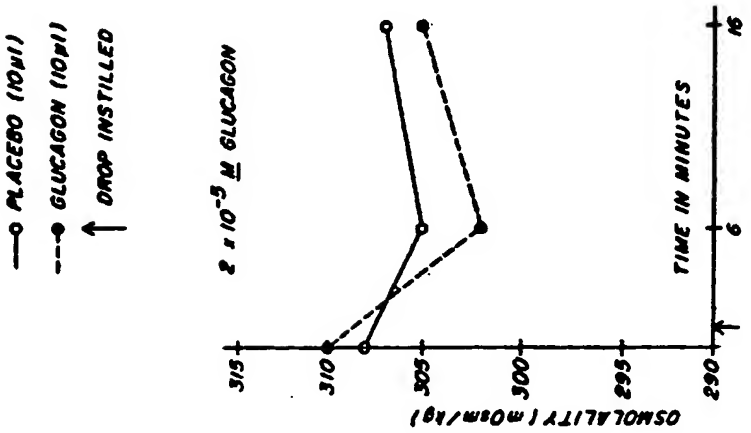

FIG. 6B

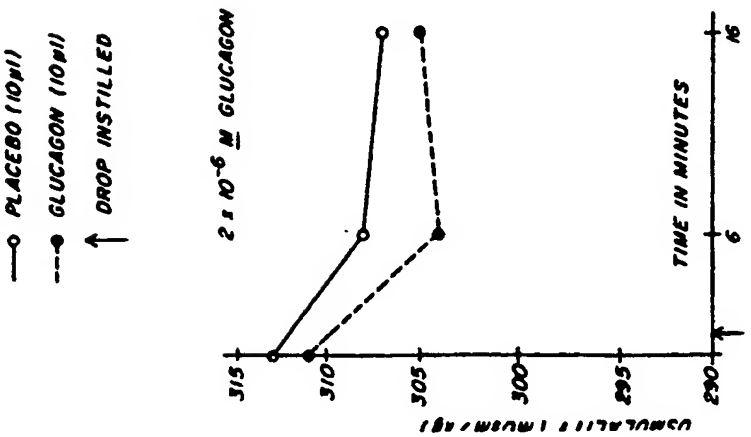

FIG. 6A

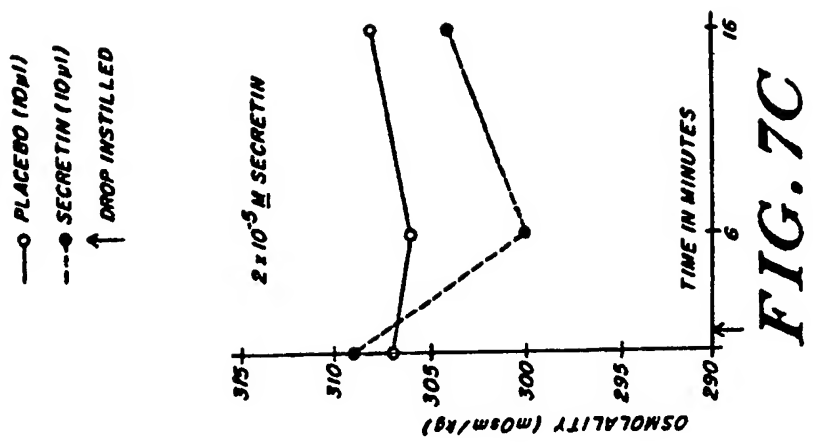

FIG. 7C

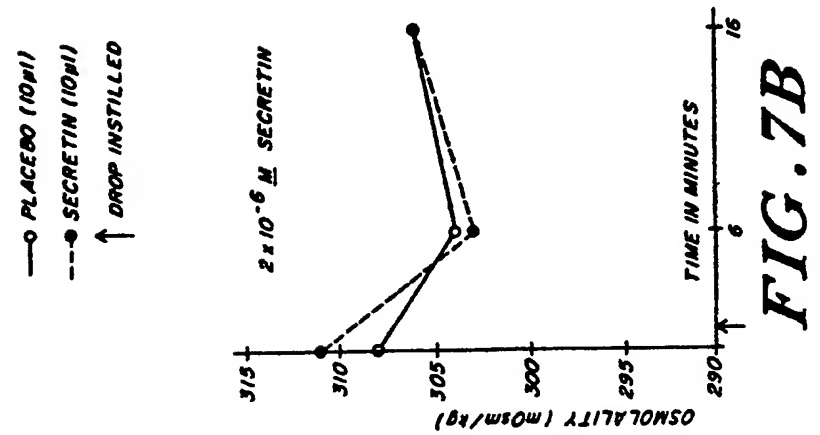

FIG. 7B

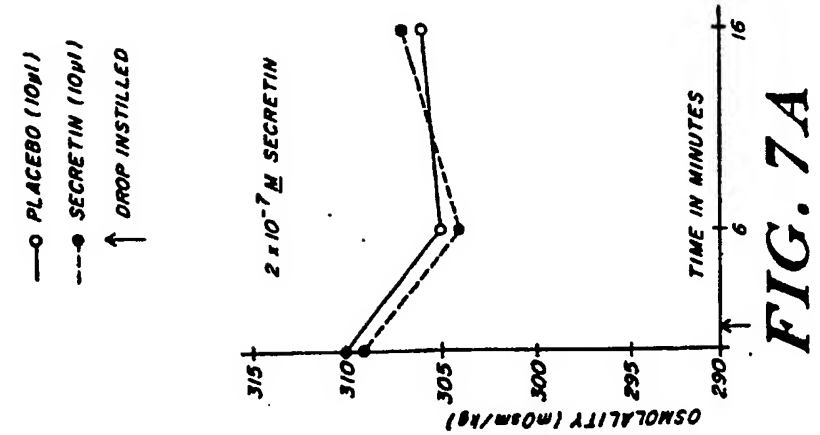

FIG. 7A